General

Guideline Title

Fertility: assessment and treatment for people with fertility problems.

Bibliographic Source(s)

National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. 63 p. (Clinical guideline; no. 156).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. London: RCOG Press; 2004 Feb. 216 p. [1151 references]

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 8, 2016 – Metformin-containing Drugs : The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Recommendations are marked as [2004], [2004, amended 2013], [2013], or [new 2013]:

- [2004] indicates that the evidence has not been updated and reviewed since 2004.
- [2004, amended 2013] indicates that the evidence has not been updated and reviewed since 2004, but a small amendment has been made to the recommendation.
- [2013] indicates that the evidence has been reviewed but no changes have been made to the recommendation.
- [new 2013] indicates that the evidence has been reviewed and the recommendation has been updated or added.

See the original guideline document for the definitions of terms used in the guideline.

Principles of Care

Providing Information

Couples who experience problems in conceiving should be seen together because both partners are affected by decisions surrounding investigation and treatment. [2004]

People should have the opportunity to make informed decisions regarding their care and treatment via access to evidence-based information. These choices should be recognised as an integral part of the decision-making process. Verbal information should be supplemented with written information or audio-visual media. [2004]

Information regarding care and treatment options should be provided in a form that is accessible to people who have additional needs, such as people with physical, cognitive, or sensory disabilities, and people who do not speak or read English. [2004]

Psychological Effects of Fertility Problems

When couples have fertility problems, both partners should be informed that stress in the male and/or female partner can affect the couple's relationship and is likely to reduce libido and frequency of intercourse which can contribute to the fertility problems. [2004, amended 2013]

People who experience fertility problems should be informed that they may find it helpful to contact a fertility support group. [2004]

People who experience fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause psychological stress. [2004]

Counselling should be offered before, during, and after investigation and treatment, irrespective of the outcome of these procedures. [2004]

Counselling should be provided by someone who is not directly involved in the management of the individual's and/or couple's fertility problems. [2004, amended 2013]

Generalist and Specialist Care

People who experience fertility problems should be treated by a specialist team because this is likely to improve the effectiveness and efficiency of treatment and is known to improve people's satisfaction with treatment. [2004, amended 2013]

Initial Advice to People Concerned about Delays in Conception

Chance of Conception

People who are concerned about their fertility should be informed that over 80% of couples in the general population will conceive within 1 year if:

- The woman is aged under 40 years and
- They do not use contraception and have regular sexual intercourse

Of those who do not conceive in the first year, about half will do so in the second year (cumulative pregnancy rate over 90%). [2004, amended 2013]

Inform people who are using artificial insemination to conceive and who are concerned about their fertility that:

- Over 50% of women aged under 40 years will conceive within 6 cycles of intrauterine insemination (IUI)
- Of those who do not conceive within 6 cycles of intrauterine insemination, about half will do so with a further 6 cycles (cumulative pregnancy rate over 75%). [new 2013]

Inform people who are using artificial insemination to conceive and who are concerned about their fertility that using fresh sperm is associated with higher conception rates than frozen–thawed sperm. However, intrauterine insemination, even using frozen–thawed sperm, is associated with higher conception rates than intracervical insemination. [new 2013]

Inform people who are concerned about their fertility that female fertility and (to a lesser extent) male fertility decline with age. [new 2013]

Discuss chances of conception with people concerned about their fertility who are:

- Having sexual intercourse (see Table 1 in the original guideline document) or
- Using artificial insemination (see Table 2 in the original guideline document). [new 2013]

Frequency and Timing of Sexual Intercourse or Artificial Insemination

People who are concerned about their fertility should be informed that vaginal sexual intercourse every 2 to 3 days optimises the chance of pregnancy. [2004, amended 2013]

People who are using artificial insemination to conceive should have their insemination timed around ovulation. [new 2013]

Alcohol

Women who are trying to become pregnant should be informed that drinking no more than 1 or 2 units of alcohol once or twice per week and avoiding episodes of intoxication reduces the risk of harming a developing fetus. [2004]

Men should be informed that alcohol consumption within the Department of Health's recommendations of 3 to 4 units per day for men is unlikely to affect their semen quality. [2004, amended 2013]

Men should be informed that excessive alcohol intake is detrimental to semen quality. [2004]

Smoking

Women who smoke should be informed that this is likely to reduce their fertility. [2004]

Women who smoke should be offered referral to a smoking cessation programme to support their efforts in stopping smoking. [2004]

Women should be informed that passive smoking is likely to affect their chance of conceiving. [2004]

Men who smoke should be informed that there is an association between smoking and reduced semen quality (although the impact of this on male fertility is uncertain), and that stopping smoking will improve their general health. [2004]

Caffeinated Beverages

People who are concerned about their fertility should be informed that there is no consistent evidence of an association between consumption of caffeinated beverages (tea, coffee, and colas) and fertility problems*. [2004]

*See related recommendation under "Prediction of IVF Success - Lifestyle Factors," below.

Obesity

Women who have a body mass index (BMI) of 30 or over should be informed that they are likely to take longer to conceive. [2004, amended 2013]

Women who have a BMI of 30 or over and who are not ovulating should be informed that losing weight is likely to increase their chance of conception. [2004, amended 2013]

Women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. [2004]

Men who have a BMI of 30 or over should be informed that they are likely to have reduced fertility. [2004, amended 2013]

Low Body Weight

Women who have a BMI of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception. [2004]

Tight Underwear

Men should be informed that there is an association between elevated scrotal temperature and reduced semen quality, but that it is uncertain whether wearing loose-fitting underwear improves fertility. [2004]

Occupation

Some occupations involve exposure to hazards that can reduce male or female fertility and therefore a specific enquiry about occupation should be made to people who are concerned about their fertility and appropriate advice should be offered. [2004]

Prescribed, Over-the-Counter, and Recreational Drug Use

A number of prescription, over-the-counter, and recreational drugs interfere with male and female fertility, and therefore a specific enquiry about these should be made to people who are concerned about their fertility and appropriate advice should be offered. [2004]

Complementary Therapy

People who are concerned about their fertility should be informed that the effectiveness of complementary therapies for fertility problems has not been properly evaluated and that further research is needed before such interventions can be recommended. [2004]

Folic Acid Supplementation

Women intending to become pregnant should be informed that dietary supplementation with folic acid before conception and up to 12 weeks' gestation reduces the risk of having a baby with neural tube defects. The recommended dose is 0.4 mg per day. For women who have previously had an infant with a neural tube defect or who are receiving anti-epileptic medication or who have diabetes (see the NICE guideline Diabetes in pregnancy. Management of diabetes and its complications from pre-conception to the postnatal period [NICE clinical guideline 63]), a higher dose of 5 mg per day is recommended. [2004, amended 2013]

Defining Infertility

People who are concerned about delays in conception should be offered an initial assessment. A specific enquiry about lifestyle and sexual history should be taken to identify people who are less likely to conceive. [2004]

Offer an initial consultation to discuss the options for attempting conception to people who are unable to, or would find it very difficult to, have vaginal intercourse. [new 2013]

The environment in which investigation of fertility problems takes place should enable people to discuss sensitive issues such as sexual abuse. [2004]

Healthcare professionals should define infertility in practice as the period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented. [new 2013]

A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. [new 2013]

A woman of reproductive age who is using artificial insemination to conceive (with either partner or donor sperm) should be offered further clinical assessment and investigation if she has not conceived after 6 cycles of treatment, in the absence of any known cause of infertility. Where this is using partner sperm, the referral for clinical assessment and investigation should include her partner. [new 2013]

Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where:

- The woman is aged 36 years or over
- There is a known clinical cause of infertility or a history of predisposing factors for infertility [new 2013]

Where treatment is planned that may result in infertility (such as treatment for cancer), early fertility specialist referral should be offered. [2004, amended 2013]

People who are concerned about their fertility and who are known to have chronic viral infections such as hepatitis B, hepatitis C or human immunodeficiency virus (HIV) should be referred to centres that have appropriate expertise and facilities to provide safe risk-reduction investigation and treatment. [2004]

Investigation of Fertility Problems and Management Strategies

Semen Analysis

The results of semen analysis conducted as part of an initial assessment should be compared with the following World Health Organization (WHO) reference values*:

- Semen volume: 1.5 ml or more
- pH: 7.2 or more
- Sperm concentration: 15 million spermatozoa per ml or more
- Total sperm number: 39 million spermatozoa per ejaculate or more
- Total motility (percentage of progressive motility and non-progressive motility): 40% or more motile or 32% or more with progressive motility
- Vitality: 58% or more live spermatozoa
- Sperm morphology (percentage of normal forms): 4% or more [2004, amended 2013]

*Please note the reference ranges are only valid for the semen analysis tests outlined by the WHO.

Screening for antisperm antibodies should not be offered because there is no evidence of effective treatment to improve fertility. [2004]

If the result of the first semen analysis is abnormal, a repeat confirmatory test should be offered. [2004]

Repeat confirmatory tests should ideally be undertaken 3 months after the initial analysis to allow time for the cycle of spermatozoa formation to be completed. However, if a gross spermatozoa deficiency (azoospermia or severe oligozoospermia) has been detected the repeat test should be undertaken as soon as possible. [2004]

Post-Coital Testing of Cervical Mucus

The routine use of post-coital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate. [2004]

Ovarian Reserve Testing

Use a woman's age as an initial predictor of her overall chance of success through natural conception (see figure 1 in the original guideline document) or with in vitro fertilisation (IVF) (see figure 2 in the original guideline document). [new 2013]

Use one of the following measures to predict the likely ovarian response to gonadotrophin stimulation in IVF:

- Total antral follicle count of less than or equal to 4 for a low response* and greater than 16 for a high response**
- Anti-Müllerian hormone of less than or equal to 5.4 pmol/l for a low response† and greater than or equal to 25.0 pmol/l for a high response‡
- Follicle-stimulating hormone greater than 8.9 IU/l for a low response and less than 4 IU/l for a high response§ [new 2013]

*Follicles of ≤5 mm measured by transvaginal ultrasound on day 3 of cycle: low response was <4 oocytes.

**Follicles of 2–10 mm measured by transvaginal ultrasound on day 3 of cycle: high response was ≥15 oocytes or ≥20 oocytes.

†Beckman Coulter assay: poor response defined as <4 oocytes or cancellation.

‡Beckman Coulter or Diagnostic Systems Limited (DSL) assays: defined high response as ≥15 oocytes to >21 oocytes.

§Long protocol of down-regulation: low response defined as <4 oocytes or cancellation; high response defined as >20 oocytes.

Do not use any of the following tests individually to predict any outcome of fertility treatment:

- Ovarian volume
- Ovarian blood flow
- Inhibin B
- Oestradiol (E2) [new 2013]

Regularity of Menstrual Cycles

Women who are concerned about their fertility should be asked about the frequency and regularity of their menstrual cycles. Women with regular monthly menstrual cycles should be informed that they are likely to be ovulating. [2004]

Women who are undergoing investigations for infertility should be offered a blood test to measure serum progesterone in the mid-luteal phase of their cycle (day 21 of a 28-day cycle) to confirm ovulation even if they have regular menstrual cycles. [2004, amended 2013]

Women with prolonged irregular menstrual cycles should be offered a blood test to measure serum progesterone. Depending upon the timing of menstrual periods, this test may need to be conducted later in the cycle (for example day 28 of a 35-day cycle) and repeated weekly thereafter until the next menstrual cycle starts. [2004]

The use of basal body temperature charts to confirm ovulation does not reliably predict ovulation and is not recommended. [2004]

Women with irregular menstrual cycles should be offered a blood test to measure serum gonadotrophins (follicle-stimulating hormone and luteinising hormone). [2004]

Prolactin Measurement

Women who are concerned about their fertility should not be offered a blood test to measure prolactin. This test should only be offered to women who have an ovulatory disorder, galactorrhoea, or a pituitary tumour. [2004]

Thyroid Function Tests

Women with possible fertility problems are no more likely than the general population to have thyroid disease and the routine measurement of thyroid function should not be offered. Estimation of thyroid function should be confined to women with symptoms of thyroid disease. [2004]

Endometrial Biopsy

Women should not be offered an endometrial biopsy to evaluate the luteal phase as part of the investigation of fertility problems because there is no evidence that medical treatment of luteal phase defect improves pregnancy rates. [2004]

Investigation of Suspected Tubal and Uterine Abnormalities

Women who are not known to have comorbidities (such as pelvic inflammatory disease, previous ectopic pregnancy, or endometriosis) should be offered hysterosalpingography (HSG) to screen for tubal occlusion because this is a reliable test for ruling out tubal occlusion, and it is less invasive and makes more efficient use of resources than laparoscopy. [2004]

Where appropriate expertise is available, screening for tubal occlusion using hysterosalpingo-contrast-ultrasonography should be considered because it is an effective alternative to hysterosalpingography for women who are not known to have comorbidities. [2004]

Women who are thought to have comorbidities should be offered laparoscopy and dye so that tubal and other pelvic pathology can be assessed at the same time. [2004]

Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established. [2004]

Testing for Viral Status

People undergoing IVF treatment should be offered testing for HIV, hepatitis B, and hepatitis C (for donor insemination see related recommendation under "Donor Insemination - Screening of Sperm Donors," below). [2004, amended 2013]

People found to test positive for one or more of HIV, hepatitis B, or hepatitis C should be offered specialist advice and counselling and appropriate clinical management. [2004, amended 2013]

Viral Transmission

For couples where the man is HIV positive, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and an HIV specialist. [new 2013]

Advise couples where the man is HIV positive that the risk of HIV transmission to the female partner is negligible through unprotected sexual intercourse when all of the following criteria are met:

- The man is compliant with highly active antiretroviral therapy (HAART)

- The man has had a plasma viral load of less than 50 copies/ml for more than 6 months
- There are no other infections present
- Unprotected intercourse is limited to the time of ovulation [new 2013]

Advise couples that if all the criteria in the previous recommendation are met, sperm washing may not further reduce the risk of infection and may reduce the likelihood of pregnancy. [new 2013]

For couples where the man is HIV positive and either he is not compliant with HAART or his plasma viral load is 50 copies/ml or greater, offer sperm washing. [new 2013]

Inform couples that sperm washing reduces, but does not eliminate, the risk of HIV transmission. [new 2013]

If couples who meet all the criteria in the recommendation on the risk of HIV transfer to the female partner, above, still perceive an unacceptable risk of HIV transmission after discussion with their HIV specialist, consider sperm washing. [new 2013]

Inform couples that there is insufficient evidence to recommend that HIV negative women use pre-exposure prophylaxis, when all the criteria in the recommendation on the risk of HIV transfer to the female partner, above, are met. [new 2013]

For partners of people with hepatitis B, offer vaccination before starting fertility treatment. [new 2013]

Do not offer sperm washing as part of fertility treatment for men with hepatitis B. [new 2013]

For couples where the man has hepatitis C, any decision about fertility management should be the result of discussions between the couple, a fertility specialist and a hepatitis specialist. [new 2013]

Advise couples who want to conceive and where the man has hepatitis C that the risk of transmission through unprotected sexual intercourse is thought to be low. [new 2013]

Men with hepatitis C should discuss treatment options to eradicate the hepatitis C with their appropriate specialist before conception is considered. [new 2013]

Susceptibility to Rubella

Women who are concerned about their fertility should be offered testing for their rubella status so that those who are susceptible to rubella can be offered vaccination. Women who are susceptible to rubella should be offered vaccination and advised not to become pregnant for at least 1 month following vaccination. [2004, amended 2013]

Cervical Cancer Screening

To avoid delay in fertility treatment a specific enquiry about the timing and result of the most recent cervical smear test should be made to women who are concerned about their fertility. Cervical screening should be offered in accordance with the national cervical screening programme guidance. [2004]

Screening for *Chlamydia trachomatis*

Before undergoing uterine instrumentation women should be offered screening for *Chlamydia trachomatis* using an appropriately sensitive technique. [2004]

If the result of a test for *Chlamydia trachomatis* is positive, women and their sexual partners should be referred for appropriate management with treatment and contact tracing. [2004]

Prophylactic antibiotics should be considered before uterine instrumentation if screening has not been carried out. [2004]

Medical and Surgical Management of Male Factor Fertility Problems

Medical Management (Male Factor Infertility)

Men with hypogonadotrophic hypogonadism should be offered gonadotrophin drugs because these are effective in improving fertility. [2004]

Men with idiopathic semen abnormalities should not be offered antioestrogens, gonadotrophins, androgens, bromocriptine, or kinin-enhancing drugs because they have not been shown to be effective. [2004]

Men should be informed that the significance of antisperm antibodies is unclear and the effectiveness of systemic corticosteroids is uncertain.

[2004]

Men with leucocytes in their semen should not be offered antibiotic treatment unless there is an identified infection because there is no evidence that this improves pregnancy rates. [2004]

Surgical Management (Male Factor Infertility)

Where appropriate expertise is available, men with obstructive azoospermia should be offered surgical correction of epididymal blockage because it is likely to restore patency of the duct and improve fertility. Surgical correction should be considered as an alternative to surgical sperm recovery and IVF. [2004]

Men should not be offered surgery for varicoceles as a form of fertility treatment because it does not improve pregnancy rates. [2004]

Management of Ejaculatory Failure

Treatment of ejaculatory failure can restore fertility without the need for invasive methods of sperm retrieval or the use of assisted reproduction procedures. However, further evaluation of different treatment options is needed. [2004]

Ovulation Disorders

Classification of Ovulatory Disorders

The WHO classifies ovulation disorders into 3 groups.

- Group I: hypothalamic pituitary failure (hypothalamic amenorrhoea or hypogonadotrophic hypogonadism)
- Group II: hypothalamic-pituitary-ovarian dysfunction (predominately polycystic ovary syndrome)
- Group III: ovarian failure

WHO Group I Ovulation Disorders

Advise women with WHO Group I anovulatory infertility that they can improve their chance of regular ovulation, conception and an uncomplicated pregnancy by:

- Increasing their body weight if they have a BMI of less than 19 and/or
- Moderating their exercise levels if they undertake high levels of exercise [new 2013]

Offer women with WHO Group I ovulation disorders pulsatile administration of gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation. [2013]

WHO Group II Ovulation Disorders

In Women with WHO Group II Ovulation Disorders Receiving First-line Treatment for Ovarian Stimulation

Advise women with WHO Group II anovulatory infertility who have a BMI of 30 or over to lose weight (see related recommendation under "Initial Advice to People Concerned about Delays in Conception - Obesity," above). Inform them that this alone may restore ovulation, improve their response to ovulation induction agents, and have a positive impact on pregnancy outcomes. [new 2013]

Offer women with WHO Group II anovulatory infertility one of the following treatments, taking into account potential adverse effects, ease and mode of use, the woman's BMI, and monitoring needed:

- Clomifene citrate or
- Metformin* or
- A combination of the above [new 2013]

For women who are taking clomifene citrate, offer ultrasound monitoring during at least the first cycle of treatment to ensure that they are taking a dose that minimises the risk of multiple pregnancy. [2013]

For women who are taking clomifene citrate, do not continue treatment for longer than 6 months. [new 2013]

Women prescribed metformin* should be informed of the side effects associated with its use (such as nausea, vomiting, and other gastrointestinal disturbances). [2004]

*At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow

relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

In Women with WHO Group II Ovulation Disorders Who Are Known to Be Resistant to Clomifene Citrate

For women with WHO Group II ovulation disorders who are known to be resistant to clomifene citrate, consider one of the following second-line treatments, depending on clinical circumstances and the woman's preference:

- Laparoscopic ovarian drilling or
- Combined treatment with clomifene citrate and metformin* if not already offered as first-line treatment or
- Gonadotrophins [new 2013]

Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation. [2004]

The use of adjuvant growth hormone treatment with gonadotrophin-releasing hormone agonist and/or human menopausal gonadotrophin during ovulation induction in women with polycystic ovary syndrome who do not respond to clomifene citrate is not recommended because it does not improve pregnancy rates. [2004]

The effectiveness of pulsatile gonadotrophin-releasing hormone in women with clomifene citrate-resistant polycystic ovary syndrome is uncertain and is therefore not recommended outside a research context. [2004]

*At the time of publication (February 2013), metformin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

Hyperprolactinaemic Amenorrhoea – Dopamine Agonists

Women with ovulatory disorders due to hyperprolactinaemia should be offered treatment with dopamine agonists such as bromocriptine. Consideration should be given to safety for use in pregnancy and minimising cost when prescribing. [2004]

Monitoring Ovulation Induction during Gonadotrophin Therapy

Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment. [2004]

Ovarian ultrasound monitoring to measure follicular size and number should be an integral part of gonadotrophin therapy to reduce the risk of multiple pregnancy and ovarian hyperstimulation. [2004]

Tubal and Uterine Surgery

Tubal Microsurgery and Laparoscopic Tubal Surgery

For women with mild tubal disease, tubal surgery may be more effective than no treatment. In centres where appropriate expertise is available it may be considered as a treatment option. [2004]

Tubal Catheterisation or Cannulation

For women with proximal tubal obstruction, selective salpingography plus tubal catheterisation, or hysteroscopic tubal cannulation, may be treatment options because these treatments improve the chance of pregnancy. [2004]

Surgery for Hydrosalpinges before In Vitro Fertilisation Treatment

Women with hydrosalpinges should be offered salpingectomy, preferably by laparoscopy, before IVF treatment because this improves the chance of a live birth. [2004]

Uterine Surgery

Women with amenorrhoea who are found to have intrauterine adhesions should be offered hysteroscopic adhesiolysis because this is likely to

restore menstruation and improve the chance of pregnancy. [2004]

Medical and Surgical Management of Endometriosis

Medical Management (Ovarian Suppression) of Endometriosis

Medical treatment of minimal and mild endometriosis diagnosed as the cause of infertility in women does not enhance fertility and should not be offered. [2004, amended 2013]

Surgical Ablation

Women with minimal or mild endometriosis who undergo laparoscopy should be offered surgical ablation or resection of endometriosis plus laparoscopic adhesiolysis because this improves the chance of pregnancy. [2004]

Women with ovarian endometriomas should be offered laparoscopic cystectomy because this improves the chance of pregnancy. [2004]

Women with moderate or severe endometriosis should be offered surgical treatment because it improves the chance of pregnancy. [2004]

Post-operative medical treatment does not improve pregnancy rates in women with moderate to severe endometriosis and is not recommended. [2004]

Unexplained Infertility

Ovarian Stimulation for Unexplained Infertility

Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole, or letrozole) to women with unexplained infertility. [new 2013]

Inform women with unexplained infertility that clomifene citrate as a stand-alone treatment does not increase the chances of a pregnancy or a live birth. [new 2013]

Advise women with unexplained infertility who are having regular unprotected sexual intercourse to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. [new 2013]

Offer IVF treatment (see related recommendations under "Access Criteria for IVF - Criteria for Referral for IVF," below) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. [new 2013]

Intrauterine Insemination

Intrauterine Insemination

Consider unstimulated intrauterine insemination as a treatment option in the following groups as an alternative to vaginal sexual intercourse:

- People who are unable to, or would find it very difficult to, have vaginal intercourse because of a clinically diagnosed physical disability or psychosexual problem who are using partner or donor sperm
- People with conditions that require specific consideration in relation to methods of conception (for example, after sperm washing where the man is HIV positive)
- People in same-sex relationships [new 2013]

For people in the previous recommendation who have not conceived after 6 cycles of donor or partner insemination, despite evidence of normal ovulation, tubal patency and semenalysis, offer a further 6 cycles of unstimulated intrauterine insemination before IVF is considered. [new 2013]

For people with unexplained infertility, mild endometriosis, or 'mild male factor infertility', who are having regular unprotected sexual intercourse:

- Do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural, or religious objections to IVF)
- Advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. [new 2013]

Prediction of IVF Success

Female Age

Inform women that the chance of a live birth following IVF treatment falls with rising female age (see figure 2 in the original guideline document). [2013]

Number of Previous Treatment Cycles

Inform people that the overall chance of a live birth following IVF treatment falls as the number of unsuccessful cycles increases. [new 2013]

Previous Pregnancy History

People should be informed that IVF treatment is more effective in women who have previously been pregnant and/or had a live birth. [2004, amended 2013]

Body Mass Index

Women should be informed that female BMI should ideally be in the range 19–30 before commencing assisted reproduction, and that a female BMI outside this range is likely to reduce the success of assisted reproduction procedures. [2004]

Lifestyle Factors

People should be informed that the consumption of more than 1 unit of alcohol per day reduces the effectiveness of assisted reproduction procedures, including IVF. [2004, amended 2013]

People should be informed that maternal and paternal smoking can adversely affect the success rates of assisted reproduction procedures, including IVF treatment. [2004, amended 2013]

People should be informed that maternal caffeine consumption has adverse effects on the success rates of assisted reproduction procedures, including IVF treatment. [2004, amended 2013]

Access Criteria for IVF

Criteria for Referral for IVF

When considering IVF as a treatment option for people with fertility problems, discuss the risks and benefits of IVF in accordance with the current Human Fertilisation and Embryology Authority Code of Practice. [new 2013]

Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise 1 episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). [new 2013]

In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. [new 2013]

In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:

- They have never previously had IVF treatment
- There is no evidence of low ovarian reserve (see related recommendation under "Investigation of Fertility Problems and Management - Ovarian Reserve Testing," above)
- There has been a discussion of the additional implications of IVF and pregnancy at this age. [new 2013]

Where investigations show there is no chance of pregnancy with expectant management and where IVF is the only effective treatment, refer the woman directly to a specialist team for IVF treatment. [new 2013]

In women aged under 40 years any previous full IVF cycle, whether self- or National Health Service (NHS)-funded, should count towards the total of 3 full cycles that should be offered by the NHS. [new 2013]

Take into account the outcome of previous IVF treatment when assessing the likely effectiveness and safety of any further IVF treatment. [new 2013]

Healthcare providers should define a cancelled IVF cycle as one where an egg collection procedure is not undertaken. However, cancelled cycles due to low ovarian reserve should be taken into account when considering suitability for further IVF treatment. [new 2013]

Procedures Used during IVF Treatment

Pre-treatment in IVF

Advise women that using pre-treatment (with either the oral contraceptive pill or a progestogen) as part of IVF does not affect the chances of having a live birth. [new 2013]

Consider pre-treatment in order to schedule IVF treatment for women who are not undergoing long down-regulation protocols. [new 2013]

Down Regulation and Other Regimens to Avoid Premature Luteinising Hormone Surges in IVF

Use regimens to avoid premature luteinising hormone surges in gonadotrophin-stimulated IVF treatment cycles. [new 2013]

Use either gonadotrophin-releasing hormone agonist down-regulation or gonadotrophin-releasing hormone antagonists as part of gonadotrophin-stimulated IVF treatment cycles. [new 2013]

Only offer gonadotrophin-releasing hormone agonists to women who have a low risk of ovarian hyperstimulation syndrome. [new 2013]

When using gonadotrophin-releasing hormone agonists as part of IVF treatment, use a long down-regulation protocol. [new 2013]

Controlled Ovarian Stimulation in IVF

Use ovarian stimulation as part of IVF treatment. [new 2013]

Use either urinary or recombinant gonadotrophins for ovarian stimulation as part of IVF treatment. [new 2013]

When using gonadotrophins for ovarian stimulation in IVF treatment:

- Use an individualised starting dose of follicle-stimulating hormone, based on factors that predict success, such as:
  - Age
  - BMI
  - Presence of polycystic ovaries
  - Ovarian reserve
- Do not use a dosage of follicle-stimulating hormone of more than 450 IU/day. [new 2013]

Offer women ultrasound monitoring (with or without oestradiol levels) for efficacy and safety throughout ovarian stimulation. [new 2013]

Inform women that clomifene citrate-stimulated and gonadotrophin-stimulated IVF cycles have higher pregnancy rates per cycle than 'natural cycle' IVF. [2013]

Do not offer women 'natural cycle' IVF treatment. [2013]

Do not use growth hormone or dehydroepiandrosterone (DHEA) as adjuvant treatment in IVF protocols. [new 2013]

Triggering Ovulation in IVF

Offer women human chorionic gonadotrophin (urinary or recombinant) to trigger ovulation in IVF treatment. [new 2013]

Offer ultrasound monitoring of ovarian response as an integral part of the IVF treatment cycle. [2013]

Clinics providing ovarian stimulation with gonadotrophins should have protocols in place for preventing, diagnosing, and managing ovarian hyperstimulation syndrome. [2004]

Oocyte and Sperm Retrieval in IVF

Women undergoing transvaginal retrieval of oocytes should be offered conscious sedation because it is a safe and acceptable method of providing analgesia. [2004]

The safe practice of administering sedative drugs published by the Academy of Medical Royal Colleges should be followed. [2004]

Women who have developed at least 3 follicles before oocyte retrieval should not be offered follicle flushing because this procedure does not increase the numbers of oocytes retrieved or pregnancy rates, and it increases the duration of oocyte retrieval and associated pain. [2004]

Surgical sperm recovery before ICSI may be performed using several different techniques depending on the pathology and wishes of the man. In

all cases, facilities for cryopreservation of spermatozoa should be available. [2004]

Assisted hatching is not recommended because it has not been shown to improve pregnancy rates. [2004]

Embryo Transfer Strategies in IVF

Women undergoing IVF treatment should be offered ultrasound-guided embryo transfer because this improves pregnancy rates. [2004]

Replacement of embryos into a uterine cavity with an endometrium of less than 5 mm thickness is unlikely to result in a pregnancy and is therefore not recommended. [2004]

Women should be informed that bed rest of more than 20 minutes' duration following embryo transfer does not improve the outcome of IVF treatment. [2004]

Evaluate embryo quality, at both cleavage and blastocyst stages, according to the Association of Clinical Embryologists and UK National External Quality Assessment Service for Reproductive Science Embryo and Blastocyst Grading schematic (see figure 3 in the original guideline document). [new 2013]

When considering the number of fresh or frozen embryos to transfer in IVF treatment:

- For women aged under 37 years:
  - In the first full IVF cycle use single embryo transfer.
  - In the second full IVF cycle use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available.
  - In the third full IVF cycle transfer no more than 2 embryos.
- For women aged 37–39 years:
  - In the first and second full IVF cycles use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos.
  - In the third full IVF cycle transfer no more than 2 embryos.
- For women aged 40–42 years consider double embryo transfer. [new 2013]

For women undergoing IVF treatment with donor eggs, use an embryo transfer strategy that is based on the age of the donor. [new 2013]

No more than 2 embryos should be transferred during any one cycle of IVF treatment. [2013]

Where a top-quality blastocyst is available, use single embryo transfer. [new 2013]

When considering double embryo transfer, advise people of the risks of multiple pregnancy associated with this strategy. [new 2013]

Offer cryopreservation to store any remaining good-quality embryos after embryo transfer. [new 2013]

Advise women who have regular ovulatory cycles that the likelihood of a live birth after replacement of frozen–thawed embryos is similar for embryos replaced during natural cycles and hormone-supplemented cycles. [2013]

Luteal Phase Support after IVF

Offer women progesterone for luteal phase support after IVF treatment. [new 2013]

Do not routinely offer women human chorionic gonadotrophin for luteal phase support after IVF treatment because of the increased likelihood of ovarian hyperstimulation syndrome. [2013]

Inform women undergoing IVF treatment that the evidence does not support continuing any form of treatment for luteal phase support beyond 8 weeks' gestation. [new 2013]

Gamete Intrafallopian Transfer and Zygote Intrafallopian Transfer

There is insufficient evidence to recommend the use of gamete intrafallopian transfer or zygote intrafallopian transfer in preference to IVF in couples with unexplained fertility problems or male factor fertility problems. [2004]

Intracytoplasmic Sperm Injection

Indications for Intracytoplasmic Sperm Injection

The recognised indications for treatment by ICSI include:

- Severe deficits in semen quality
- Obstructive azoospermia
- Non-obstructive azoospermia

In addition, treatment by ICSI should be considered for couples in whom a previous IVF treatment cycle has resulted in failed or very poor fertilisation. [2004]

Genetic Issues and Counselling

Before considering treatment by ICSI, people should undergo appropriate investigations, both to establish a diagnosis and to enable informed discussion about the implications of treatment. [2004, amended 2013]

Before treatment by ICSI consideration should be given to relevant genetic issues. [2004]

Where a specific genetic defect associated with male infertility is known or suspected couples should be offered appropriate genetic counselling and testing. [2004]

Where the indication for ICSI is a severe deficit of semen quality or nonobstructive azoospermia, the man's karyotype should be established. [2004]

Men who are undergoing karyotype testing should be offered genetic counselling regarding the genetic abnormalities that may be detected. [2004]

Testing for Y chromosome microdeletions should not be regarded as a routine investigation before ICSI. However, it is likely that a significant proportion of male infertility results from abnormalities of genes on the Y chromosome involved in the regulation of spermatogenesis, and couples should be informed of this. [2004]

Intracytoplasmic Sperm Injection Versus IVF

Couples should be informed that ICSI improves fertilisation rates compared to IVF alone, but once fertilisation is achieved the pregnancy rate is no better than with IVF. [2004]

Donor Insemination

Indications for Donor Insemination

The use of donor insemination is considered effective in managing fertility problems associated with the following conditions:

- Obstructive azoospermia
- Non-obstructive azoospermia
- Severe deficits in semen quality in couples who do not wish to undergo ICSI. [2004, amended 2013]

Donor insemination should be considered in conditions such as:

- Where there is a high risk of transmitting a genetic disorder to the offspring
- Where there is a high risk of transmitting infectious disease to the offspring or woman from the man
- Severe rhesus isoimmunisation [2004, amended 2013]

Information and Counselling

Couples should be offered information about the relative merits of ICSI and donor insemination in a context that allows equal access to both treatment options. [2004]

Couples considering donor insemination should be offered counselling from someone who is independent of the treatment unit regarding all the physical and psychological implications of treatment for themselves and potential children. [2004]

Screening of Sperm Donors

Units undertaking semen donor recruitment and the cryopreservation of donor spermatozoa for treatment purposes should follow the 'UK guidelines for the medical and laboratory screening of sperm, egg, and embryo donors' (2008)* describing the selection and screening of donors. [2004, amended 2013]

All potential semen donors should be offered counselling from someone who is independent of the treatment unit regarding the implications for themselves and their genetic children, including any potential children resulting from donated semen. [2004]

*This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians and Gynaecologists.

Assessments to Offer the Woman

Before starting treatment by donor insemination (for conditions listed in the related recommendations under "Donor Insemination - Indications for donor insemination," above) it is important to confirm that the woman is ovulating. Women with a history that is suggestive of tubal damage should be offered tubal assessment before treatment. [2004, amended 2013]

Women with no risk factors in their history should be offered tubal assessment after 3 cycles if treatment by donor insemination (for conditions listed in the related recommendations under "Donor Insemination - Indications for Donor Insemination," above) has been unsuccessful. [2004, amended 2013]

Intrauterine Insemination Versus Intracervical Insemination

Couples using donor sperm should be offered intrauterine insemination in preference to intracervical insemination because it improves pregnancy rates. [2004]

Unstimulated Versus Stimulated Donor Insemination

Women who are ovulating regularly should be offered a minimum of 6 cycles of donor insemination (for conditions listed in the related recommendations under "Donor Insemination - Indications for Donor Insemination," above) without ovarian stimulation to reduce the risk of multiple pregnancy and its consequences. [2004, amended 2013]

Oocyte Donation

Indications for Oocyte Donation

The use of donor oocytes is considered effective in managing fertility problems associated with the following conditions:

- Premature ovarian failure
- Gonadal dysgenesis including Turner syndrome
- Bilateral oophorectomy
- Ovarian failure following chemotherapy or radiotherapy
- Certain cases of IVF treatment failure

Oocyte donation should also be considered in certain cases where there is a high risk of transmitting a genetic disorder to the offspring. [2004]

Screening of Oocyte Donors

Before donation is undertaken, oocyte donors should be screened for both infectious and genetic diseases in accordance with the 'UK guidelines for the medical and laboratory screening of sperm, egg, and embryo donors' (2008)*. [2004, amended 2013]

*This recommendation has been updated to reflect a new guideline issued by the joint working party of Association of Biomedical Andrologists, Association of Clinical Embryologists, British Andrology Society, British Fertility Society and Royal College of Obstetricians and Gynaecologists.

Oocyte Donation and 'Egg Sharing'

Oocyte donors should be offered information regarding the potential risks of ovarian stimulation and oocyte collection. [2004]

Oocyte recipients and donors should be offered counselling from someone who is independent of the treatment unit regarding the physical and psychological implications of treatment for themselves and their genetic children, including any potential children resulting from donated oocytes. [2004]

All people considering participation in an 'egg-sharing' scheme should be counselled about its particular implications. [2004]

People with Cancer Who Wish to Preserve Fertility

Cryopreservation of Semen, Oocytes, and Embryos

When considering and using cryopreservation for people before starting chemotherapy or radiotherapy that is likely to affect their fertility, follow recommendations in *The effects of cancer treatment on reproductive functions* (2007)*. [2013]

At diagnosis, the impact of the cancer and its treatment on future fertility should be discussed between the person diagnosed with cancer and their cancer team. [new 2013]

When deciding to offer fertility preservation to people diagnosed with cancer, take into account the following factors:

- Diagnosis
- Treatment plan
- Expected outcome of subsequent fertility treatment
- Prognosis of the cancer treatment
- Viability of stored/post-thawed material [new 2013]

For cancer-related fertility preservation, do not apply the eligibility criteria used for conventional infertility treatment. [new 2013]

Do not use a lower age limit for cryopreservation for fertility preservation in people diagnosed with cancer. [new 2013]

Inform people diagnosed with cancer that the eligibility criteria used in conventional infertility treatment do not apply in the case of fertility cryopreservation provided by the National Health Service. However, those criteria will apply when it comes to using stored material for assisted conception in a National Health Service setting. [new 2013]

When using cryopreservation to preserve fertility in people diagnosed with cancer, use sperm, embryos, or oocytes. [new 2013]

Offer sperm cryopreservation to men and adolescent boys who are preparing for medical treatment for cancer that is likely to make them infertile. [new 2013]

Use freezing in liquid nitrogen vapour as the preferred cryopreservation technique for sperm. [new 2013]

Offer oocyte or embryo cryopreservation as appropriate to women of reproductive age (including adolescent girls) who are preparing for medical treatment for cancer that is likely to make them infertile if:

- They are well enough to undergo ovarian stimulation and egg collection and
- This will not worsen their condition and
- Enough time is available before the start of their cancer treatment [new 2013]

In cryopreservation of oocytes and embryos, use vitrification instead of controlled-rate freezing if the necessary equipment and expertise is available. [new 2013]

Store cryopreserved material for an initial period of 10 years. [new 2013]

Offer continued storage of cryopreserved sperm, beyond 10 years, to men who remain at risk of significant infertility. [new 2013]

*Royal College of Physicians, The Royal College of Radiologists, Royal College of Obstetricians and Gynaecologists. (2007) The effects of cancer treatment on reproductive functions: guidance on management. Report of a Working Party. London: RCP.

Long-term Safety of Assisted Reproductive Technologies for Women with Infertility and Their Children

Long-term Health Outcomes of Ovulation Induction and Ovarian Stimulation

Give people who are considering ovulation induction or ovarian stimulation up-to-date information about the long-term health outcomes of these treatments. [new 2013]

Inform women who are offered ovulation induction or ovarian stimulation that:

- No direct association has been found between these treatments and invasive cancer and
- No association has been found in the short- to medium-term between these treatments and adverse outcomes (including cancer) in children born from ovulation induction and
- Information about long-term health outcomes in women and children is still awaited. [new 2013]

Limit the use of ovulation induction or ovarian stimulation agents to the lowest effective dose and duration of use. [new 2013]

Long-term Health Outcomes and Safety of IVF

Give people who are considering IVF treatment, with or without ICSI, up-to-date information about the long-term health outcomes (including the consequences of multiple pregnancy) of these treatments. [new 2013]

Inform women that while the absolute risks of long-term adverse outcomes of IVF treatment, with or without ICSI, are low, a small increased risk of borderline ovarian tumours cannot be excluded. [new 2013]

Inform people who are considering IVF treatment that the absolute risks of long-term adverse outcomes in children born as result of IVF are low. [new 2013]

Limit drugs used for controlled ovarian stimulation in IVF treatment to the lowest effective dose and duration of use. [new 2013]

Clinical Algorithm(s)

The full version of the original guideline document includes a care pathway/algorithm for overall care.

In addition, a NICE pathway on fertility is available at the National Institute for Health and Clinical Excellence Web site .

Scope

Disease/Condition(s)

- Infertility
- Fertility problems

Guideline Category

Counseling

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Obstetrics and Gynecology

Surgery

Urology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Patients

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To offer best practice advice on assisting people of reproductive age who have problems conceiving

Target Population

People of reproductive age who have problems conceiving, including:

- People with explained or unexplained infertility
- People in same-sex relationships who have unexplained infertility after donor insemination
- People who are unable to, or would find it very difficult to, or who have been advised not to have heterosexual intercourse
- People with conditions or disabilities that require specific consideration in relation to methods of conception
- People who are preparing for cancer treatment who may wish to preserve their fertility

Note: This guideline does not include the management of people with the following clinical issues:

Multiple or recurrent miscarriage
Surrogacy

Interventions and Practices Considered

Diagnosis/Evaluation of Fertility Problems

1. Semen analysis, including volume, pH, sperm concentration, total sperm number, motility, vitality, and morphology
2. Post-coital testing of cervical mucosa (not recommended)
3. Ovarian reserve testing
4. Evaluation of regularity of women's menstrual cycles
    - Asking about frequency and regularity of menstrual cycle
    - Blood test to measure serum progesterone to confirm ovulation
    - Use of basal body temperature charts to confirm ovulation (not recommended)
5. Blood test to measure serum gonadotrophins (follicle-stimulating hormone and luteinising hormone)
6. Blood test to measure prolactin, thyroid function tests, endometrial biopsy (not recommended routinely in fertility investigations)
7. Investigation of suspected tubal and uterine abnormalities
    - Hysterosalpingography (HSG) or hysterosalpingo-contrast-ultrasonography to screen for tubal occlusion
    - Laparoscopy and dye to assess for tubal and other pelvic pathology
8. Testing for human immunodeficiency virus (HIV), hepatitis B, and hepatitis C in people undergoing in vitro fertilisation procedures and offering counselling and advice for those with positive tests
9. Testing for rubella in women
10. Cervical cancer screening
11. Screening for *Chlamydia trachomatis*

Treatment/Management

1. Principles of care
    - Providing information through couple-centred management
    - Describing psychological effects of fertility problems
    - Providing specialist and generalist care
2. Providing initial advice to people concerned about delays in conception regarding chance of conception and factors that influence fertility
3. Medical and surgical management of male factor fertility problems
    - Gonadotrophin drugs for hypogonadotrophic hypogonadism
    - Antioestrogens, gonadotrophins, androgens, bromocriptine, or kinin-enhancing drugs (not recommended for idiopathic semen abnormalities)
    - Surgical correction of epididymal blockage
    - Surgery for varicoceles (not recommended)
    - Management of ejaculatory failure
4. Management of ovulation disorders
    - Classification of ovulatory disorders
    - Advice on increasing body weight and moderating exercise levels in women with Group I ovulation disorders; losing weight in women with group II ovulation disorders
    - Gonadotrophin-releasing hormone or gonadotrophins with luteinising hormone activity to induce ovulation
    - Clomifene citrate or metformin or combination
    - Laparoscopic ovarian drilling
    - Dopamine agonists such as bromocriptine for hyperprolactinaemic amenorrhoea
    - Ultrasound monitoring during ovulation induction
5. Tubal and uterine surgery
6. Medical and surgical management of endometriosis
7. Management of unexplained infertility
8. Unstimulated intrauterine insemination for specific populations
9. In vitro fertilisation (IVF)
    - Predicting IVF success and criteria for referral for IVF
    - Down regulation and other regimens to avoid premature luteinising hormone surges in IVF
    - Controlled ovarian stimulation in IVF
    - Triggering ovulation in IVF with human chorionic gonadotrophin (urinary or recombinant)
    - Oocyte and sperm retrieval in IVF
    - Embryo transfer strategies in IVF
    - Use of progesterone for luteal phase support after IVF
    - Gamete intrafallopian transfer and zygote intrafallopian transfer (insufficient evidence to recommend)
10. Intracytoplasmic sperm injection (ICSI), including consideration of genetic issues and counselling before ICSI
11. Donor insemination
    - Information and counselling on relative merits of ICSI and donor insemination
    - Screening of sperm donors
    - Assessments to offer women before starting donor insemination
    - Use of intrauterine insemination versus intracervical insemination
    - Use of unstimulated versus stimulated donor insemination
12. Oocyte donation, including donor screening and counselling regarding egg sharing
13. Cryopreservation of semen, oocytes, and embryos
14. Counselling on long-term safety of assisted reproductive technologies for women with infertility and their children

Major Outcomes Considered

- Live full-term singleton birth
- Patient satisfaction
- Anxiety and/or depression
- Multiple births
- Fetal abnormalities
- Adverse pregnancy outcomes (including ectopic pregnancy, miscarriage, fetal growth restriction, spontaneous preterm delivery, perinatal death, pre-eclampsia, and gestational diabetes)

- Ovarian hyperstimulation syndrome (OHSS)
- Long-term effects on the woman of ovulation induction
- Long-term effects on children born as a result of assisted reproduction techniques
- Multiple pregnancy
- Health related quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing Review Questions and Protocols and Identifying Evidence

The Guideline Development Group formulated review questions based on the scope (see Appendix A of the full version of the original guideline document; see the "Availability of Companion Documents" field) and prepared a protocol for each review question (see Appendix D of the full version of the original guideline document). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix E of the full version of the original guideline document) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases, the National Health Service (NHS) Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. None of the searches were limited by date. Searches in Embase were limited to English language and searches in Medline were limited to English language and studies in humans. None of the other searches were limited by language of publication (although publications in languages other than English were not reviewed). Validated search filters were used to identify particular study designs, such as randomised controlled trials. There was no systematic attempt to search grey literature (conference abstracts, theses, or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 30 November 2011.

Number of Source Documents

The number of studies identified for each clinical question is provided in Appendix F of the full guideline document (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in GRADE (Grading of Recommendations Assessment, Development and Evaluation)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
Very Low	Any estimate of effect is very uncertain

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Clinical Evidence

Reviewing and Synthesising Evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below, and an overall quality rating (high, moderate, low, or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating)
- Limitations in the design or execution of the study including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating)
- Inconsistency of effects across studies (this can reduce the quality rating)
- Indirectness: the extent to which the available evidence fails to address the specific review question (this can reduce the quality rating)
- Imprecision: reflects the confidence in the estimate of effect (this can reduce the quality rating)
- Other considerations including large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect (these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of randomised controlled trials (RCTs), or an individual RCT. In the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low, or very low if factors listed above are not addressed adequately. For issues of prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis, or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the accuracy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was considered optimal. For studies

evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratios for positive and negative test results (LR+ and LR–, respectively) were calculated or quoted where possible (see Table 3.3 in the full version of the original guideline document). The only additional approach was used in the section on ovarian reserve testing where there were two parts to the review (see Section 6.3 in the full version of the original guideline document). The first part was to assess all available tests for ovarian reserve against pre-specified quality criteria for specified outcomes determined by the Guideline Development Group (GDG). The quality criterion was a receiver operator characteristic 'area under the curve' (ROC-AUC) of 0.8 or more (based on Hosmer and Lemeshow test). Tests that met this criterion were then included in the second part of the review where more detailed assessment was undertaken and likelihood ratios were calculated for each test and the specified outcomes.

The GRADE system described above covers studies of treatment effectiveness. However, it is less well established for studies reporting accuracy of diagnostic tests. For such studies, NICE recommends using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) methodology checklist to assess study quality (see the NICE guidelines manual, 2009; see the "Availability of Companion Documents" field).

Some studies were excluded from the guideline reviews after obtaining copies of the publications because they did not meet inclusion criteria specified by the GDG (see Appendix G of the full version of the original guideline document). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix H of the full version of the original guideline document). Where possible, dichotomous outcomes were presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences with 95% CIs or standard deviations (SDs).

The body of evidence identified for each therapy or treatment review question (or part of a review question) was presented in the form of a GRADE evidence profile summarising the quality of the evidence and the findings (pooled relative and absolute effect sizes and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled RRs, pooled ORs or weighted mean differences. By default, meta-analyses were conducted by fitting fixed effects models, but where statistically significant heterogeneity was identified, random effects models were used to investigate the impact of the heterogeneity. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies) the range of effect sizes reported in the included studies was presented. The GRADE evidence profiles are not directly applicable to epidemiological studies or non-comparative cohort studies. Where these studies are presented, they are done so in descriptive paragraphs and/or tables as appropriate.

Outcome Measures

For this guideline update, the management of fertility problems has been assessed against a variety of reproductive and pregnancy outcomes. The justification for using these outcomes is based on their relevance to people covered by the guideline and consensus among members of the GDG. Outcomes include those that were felt to be desirable (for example a live birth) and unwanted effects of treatment that it would be important to reduce to a minimum (for example ovarian hyperstimulation syndrome). When assessing the effectiveness of a particular treatment, information about the effect of that treatment on one or more primary outcomes was sought (see the "Major Outcomes Considered" field).

When considering the evidence, the GDG judged 'live full-term singleton birth' to be the most important outcome as the group believes it to be the best indicator of a healthy mother and of a 'healthy baby', and therefore the best indicator of successful in vitro fertilisation treatment. 'Full term' was included in the outcome as babies born at term are more likely to survive without disability than babies born preterm. As many studies did not report live full-term singleton births, the number of live births or the number of singleton births were often used instead of live full-term singleton birth, with the data accordingly downgraded for indirectness in the GRADE profiles.

'Clinical pregnancy' was also identified as an important outcome and was used in conjunction with the live full-term singleton birth data. Clinical pregnancy was also used when a study did not report live birth data, although the GDG acknowledged that not all clinical pregnancies result in a live birth. If a study did not define clinical pregnancy, its data was also downgraded for indirectness.

Incorporating Health Economics

The GDG prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature are presented alongside the clinical effectiveness reviews in the full version of the original guideline document.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were:

- The effectiveness of intrauterine insemination (see Chapter 12 of the full version of the original guideline document)
- The cost effectiveness of in vitro fertilisation treatment (see Chapter 14 of the full version of the original guideline document)
- The effectiveness and safety of different embryo/blastocyst transfer strategies (see Section 15.7 of the full version of the original guideline document).

Methods Used to Formulate the Recommendations

Expert Consensus (Nominal Group Technique)

Informal Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

This guidance was commissioned by NICE and developed in accordance with the guideline development process outlined in the 2009 edition of The Guidelines Manual (see the "Availability of Companion Documents" field).

As this is a partial update of the original guideline only specific topics are addressed, which are:

- Tests for ovarian reserve
- Effectiveness of ovulation induction agents used in treatment programmes for infertility
- Effectiveness of intrauterine insemination, with or without ovulation induction agents
- Multifactorial prediction of success to determine clinical and cost effectiveness criteria for in vitro fertilisation (IVF) treatment
- Effectiveness of the following IVF treatment strategies:
    - Pretreatment
    - Down-regulation and other regimens to avoid premature luteinising hormone surges in IVF
    - Ovarian stimulation (including mild versus conventional stimulation)
    - Triggering
    - Timing and number of embryo transfer
    - Luteal phase support
- Cryopreservation and vitrification to preserve fertility for patients with impending cancer treatment
- Appropriate management of couples where the male partner is human immunodeficiency virus (HIV) positive and female is HIV negative (including sperm washing)
- Long-term safety of ovulation induction and ovarian stimulation agents in women and children
- The long-term safety of IVF in women with infertility and their children

In addition, a considerable amount of relevant guidance has been published since 2004, and this update will cross-reference this (including the World Health Organization reference values for semen analysis and the Human Fertilisation and Embryology Authority Code of Practice), where appropriate.

Evidence to Recommendations

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the Guideline Development group (GDG) to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. In the case of the topic on the number of embryos to be transferred during IVF, a formal consensus approach was used (see "Specific Considerations for This Guideline," below, and Section 15.7 of the full version of the original guideline document). Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- Relative value placed on the outcomes considered
- Consideration of clinical benefits and harms
- Consideration of net health benefits and resource use

- Quality of the evidence
- Other considerations (including equalities issues)

In areas where no substantial clinical research evidence was identified, the GDG members considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of National Health Service resources (interventions) was considered was based on GDG consensus in relation to the likely cost effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer its review questions was lacking and used this information to formulate recommendations for future research.

Where no agreement could be reached on a recommendation by the GDG, a formal vote was undertaken and a majority decision was taken forward in the recommendations.

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the GDG throughout the development process and specifically addressed in individual recommendations where relevant.

Specific Considerations for This Guideline

Formal Consensus Survey

A formal consensus survey was used to define embryo transfer strategies, as it was agreed that a recommendation was needed but the GDG was unable to reach a conclusion using discussion alone.

Methods

The formal consensus approach involved a series of action statements relating to management or treatment under review being drafted by the NCC-WCH technical team. These were collated into a consensus questionnaire. The GDG members were asked to independently complete the questionnaire stating their level of agreement (ranging from 'Strongly agree' to 'Strongly disagree') with each statement and provide comments on where statements should be amended. The results of the voting were collated by the technical team. If 70% or more of the GDG members agreed or disagreed with a statement then it was concluded that consensus had been reached. If there was no consensus the statement could be adapted based on comments and presented for a second round of voting, applying the same majority threshold. Statements where consensus was reached were then used to draft recommendations. These were discussed and ratified at a subsequent GDG meeting.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Note: The National Institutes for Health and Clinical Excellence (NICE) began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations shaded in grey in the original guideline document and ending [2004]. In particular, for recommendations labelled [2004] the word 'consider' may not necessarily be used to denote the strength of the recommendation.

Cost Analysis

The aims of the health economic input to the guideline were to inform the Guideline Development Group (GDG) of potential economic issues relating to fertility, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms, and costs of different care options.

The GDG prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature are presented alongside the clinical effectiveness reviews.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were:

- The effectiveness of intrauterine insemination (IUI) (see Chapter 12 in the full version of the guideline [see the "Availability of Companion Documents" field])
- The cost effectiveness of in vitro fertilisation (IVF) treatment (see Chapter 14 in the full version of the guideline)
- The effectiveness and safety of different embryo/blastocyst transfer strategies (see Section 15.7).

See also the "Consideration of Health Benefits and Resource Uses" sections in the full version of the guideline.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Women's and Children's Health (NCC-WCH) on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. Stakeholder organisations were also invited to undertake a pre-publication check of the final guideline to identify factual inaccuracies. The Guideline Development Group carefully considered and responded to all comments received from stakeholder organisations. The comments and responses, which were reviewed independently by the National Institute for Health and Clinical Excellence (NICE), are published on the NICE website.

As part of NICE's quality assurance process, the guideline documentation and responses to stakeholders undergo final editorial checks and review by the quality assurance panel. At this point the response to a particular set of stakeholder comments, and the related removal of a recommendation, was queried. The National Collaborating Centre for Women's and Children's Health (NCC-WCH) and the Guideline Development Group provided a detailed explanation of the reasons for the response. It was not possible to resolve the issue with written communication. Therefore, taking into account the stakeholder comments and quality assurance feedback, NICE convened a meeting of the Guideline Development Group to further review the wording of the recommendation. These steps are consistent with the guidance provided by the NICE Guidelines Manual.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate assessment and treatment of fertility problems

See the "Consideration of clinical benefits and harms" sections of the full version of the original guideline document for additional details about benefits of specific interventions.

Potential Harms

- Women with polycystic ovary syndrome who are being treated with gonadotrophins should not be offered treatment with gonadotrophin-releasing hormone agonist concomitantly because it does not improve pregnancy rates, and it is associated with an increased risk of ovarian hyperstimulation.
- Women prescribed metformin should be informed of the side effects associated with its use (such as nausea, vomiting, and other gastrointestinal disturbances).
- The guideline developer group (GDG) view was that clinicians need to be aware of the increased risk of ovarian hyperstimulation syndrome (OHSS) with the use of gonadotropin-releasing hormone (GnRH) agonists compared with the lower risks with the use of GnRH antagonists. The GDG acknowledged that the risk of OHSS is also dependent on which gonadotrophins and ovulation trigger are used during other parts of the in vitro fertilisation (IVF) treatment cycle, and so it would not be appropriate to recommend against the use of GnRH agonists. However, there is a need to balance the increased chance of achieving a clinical pregnancy using GnRH agonist with the increased risk of OHSS. Therefore the GDG recommended the use of either GnRH agonist or GnRH antagonist for down-regulation, but emphasised that GnRH agonist should only be used in women with a low risk of OHSS.
- The GDG acknowledged that, compared with unstimulated IVF, there is an increased risk of OHSS when ovarian stimulation takes place. The GDG agreed that it is important to continue to assess the risk of OHSS throughout IVF treatment using ultrasound monitoring. The use of an ovulation trigger further increases the risk of OHSS.
- Although the evidence showed that, when compared with GnRH agonist, human chorionic gonadotrophin resulted in more cases of OHSS, the GDG acknowledged that the absolute number of cases was low.
- Women who are offered ovulation induction with gonadotrophins should be informed about the risk of multiple pregnancy and ovarian hyperstimulation before starting treatment.
- Inform women that while the absolute risks of long-term adverse outcomes of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), are low, a small increased risk of borderline ovarian tumours cannot be excluded.
- The theoretical risk of transmitting prion disease, however unlikely, must always be considered when medicinal products are derived from or contain materials of human or bovine origin. In the case of gonadotrophins, such theoretical risks could arise from the human source material used to manufacture urinary-derived products or from bovine reagents used in the manufacture of recombinant products. However, there is no evidence of transmission of prion disease by any gonadotrophin.
- Whether ICSI treatment of infertile couples with normal karyotypes increases the occurrence of chromosomal abnormalities in offspring is unclear. Sons of infertile males with Y chromosome microdeletions will probably inherit the same abnormality and are therefore likely to be infertile. Males with no known genetic cause for severely compromised sperm quality may also father sons with Y chromosome microdeletions.

See the "Consideration of clinical benefits and harms" sections of the full version of the original guideline document for additional details about harms of specific interventions.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summaries of product characteristics of any drugs.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.
- This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information. Where recommendations have been made for the use of drugs outside their licensed indications ('off-label use'), these drugs are marked with a footnote in the recommendations.
- Patients and healthcare professionals have rights and responsibilities as set out in the National Health Service Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent and the code of practice that accompanies the Mental Capacity Act. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.
- NICE has produced guidance on the components of good patient experience in adult National Health Service services. All healthcare professionals should follow the recommendations in Patient experience in adult National Health Service services.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also Patient-centred care).

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Clinical Excellence (NICE) has developed tools to help organisations implement this guidance. These are available on the NICE Web site ; see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

Defining Infertility

- A woman of reproductive age who has not conceived after 1 year of unprotected vaginal sexual intercourse, in the absence of any known cause of infertility, should be offered further clinical assessment and investigation along with her partner. [new 2013]
- Offer an earlier referral for specialist consultation to discuss the options for attempting conception, further assessment and appropriate treatment where:
    - The woman is aged 36 years or over
    - There is a known clinical cause of infertility or a history of predisposing factors for infertility [new 2013]

Unexplained Infertility

- Do not offer oral ovarian stimulation agents (such as clomifene citrate, anastrozole, or letrozole) to women with unexplained infertility. [new 2013]
- Offer IVF treatment (see related recommendations under "Criteria for Referral for IVF," below) to women with unexplained infertility who have not conceived after 2 years (this can include up to 1 year before their fertility investigations) of regular unprotected sexual intercourse. [new 2013]

Intrauterine Insemination

For people with unexplained infertility, mild endometriosis, or 'mild male factor infertility', who are having regular unprotected sexual intercourse:

- Do not routinely offer intrauterine insemination, either with or without ovarian stimulation (exceptional circumstances include, for example, when people have social, cultural, or religious objections to in vitro fertilisation [IVF])
- Advise them to try to conceive for a total of 2 years (this can include up to 1 year before their fertility investigations) before IVF will be considered. [new 2013]

Criteria for Referral for IVF

- Inform people that normally a full cycle of IVF treatment, with or without intracytoplasmic sperm injection (ICSI), should comprise one episode of ovarian stimulation and the transfer of any resultant fresh and frozen embryo(s). [new 2013]
- In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles. [new 2013]
- In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI, provided the following 3 criteria are fulfilled:
  - They have never previously had IVF treatment.
  - There is no evidence of low ovarian reserve (see related recommendation under "Investigation of Fertility Problems and Management Strategies - Ovarian Reserve Testing" in the "Major Recommendations" field).
  - There has been a discussion of the additional implications of IVF and pregnancy at this age. [new 2013]

Embryo Transfer Strategies in IVF

- When considering the number of fresh or frozen embryos to transfer in IVF treatment:
  - For women aged under 37 years:
    - In the first full IVF cycle use single embryo transfer.
    - In the second full IVF cycle use single embryo transfer if 1 or more top-quality embryos are available. Consider using 2 embryos if no top-quality embryos are available.
    - In the third full IVF cycle transfer no more than 2 embryos.
  - For women aged 37–39 years:
    - In the first and second full IVF cycles use single embryo transfer if there are 1 or more top-quality embryos. Consider double embryo transfer if there are no top-quality embryos.
    - In the third full IVF cycle transfer no more than 2 embryos.
  - For women aged 40–42 years consider double embryo transfer. [new 2013]
- Where a top-quality blastocyst is available, use single embryo transfer. [new 2013]

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. 63 p. (Clinical guideline; no. 156).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2004 Feb (revised 2013 Feb)

Guideline Developer(s)

National Collaborating Centre for Women's and Children's Health - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

All Guideline Development Group members' interests were recorded in a standard form that covered consultancies, fee-paid work, share-holdings, fellowships, and healthcare industry in accordance with guidance from the National Institute for Clinical Excellence (NICE). The Guideline Development Group's interests are listed in Appendix C of the full version of the original guideline document.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Collaborating Centre for Women's and Children's Health. Fertility: assessment and treatment for people with fertility problems. London: RCOG Press; 2004 Feb. 216 p. [1151 references]

Guideline Availability

Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following is available:

- Fertility: assessment and treatment for people with fertility problems. Full guideline. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. 555 p. (Clinical guideline; no. 156). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .
- Fertility: assessment and treatment for people with fertility problems. Appendices. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .
- Fertility: assessment and treatment for people with fertility problems. Baseline assessment tool. (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available from the NICE Web site .
- Fertility: assessment and treatment for people with fertility problems. Clinical audit tools. (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available from the NICE Web site .
- Fertility: assessment and treatment for people with fertility problems. Costing report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. 39 p. (Clinical guideline; no. 156). Electronic copies: Available in Portable Document Format (PDF) from the NICE Web site .
- Fertility: assessment and treatment for people with fertility problems. Costing template. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available from the NICE Web site .
- Fertility. Podcast. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available from the NICE Web site .
- Fertility overview. NICE pathway. (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available from the NICE Web site .
- The guidelines manual 2009. London (UK): National Institute for Health and Clinical Excellence (NICE); 2009 Jan. Electronic copies: Available in Portable Document Format (PDF) from the NICE Archive Web site .

Patient Resources

The following is available:

- Information for the public: assessment and treatment for people with fertility problems. London (UK): National Institute for Health and Clinical Excellence (NICE); 2013 Feb. (Clinical guideline; no. 156). Electronic copies: Available from the National Institute for Health and Clinical Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI on August 27, 2004. The information was reaffirmed by the guideline developer on May 18, 2009 and updated by ECRI Institute on March 31, 2010. This summary was updated by ECRI Institute on April 16, 2013. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

The National Institute for Health and Clinical Excellence (NICE) has granted the National Guideline Clearinghouse (NGC) permission to include summaries of their clinical guidelines with the intention of disseminating and facilitating the implementation of that guidance. NICE has not yet verified this content to confirm that it accurately reflects that original NICE guidance and therefore no guarantees are given by NICE in this regard. All NICE clinical guidelines are prepared in relation to the National Health Service in England and Wales. NICE has not been involved in the development or adaptation of NICE guidance for use in any other country. The full versions of all NICE guidance can be found at www.nice.org.uk.

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